COLORECTAL CANCER DIAGNOSIS AND THERAPEUTIC UPDATES

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FOREWORD

Given the gap in the comprehensive book on ***"Colorectal cancer diagnosis and therapeutic updates, and the new findings"***, the writers agreed to discuss as many key issues regarding colorectal cancer, its management, and therapeutic progress as necessary. This book is also unique in that it contains new information about IncRNA NLIPMT inhibitors and therapeutic use in the treatment of colorectal cancer. Another reason is the presence of several detailed chapters as well as a large number of appropriate illustrations. It is anticipated that after reading this book, the reader would have acquired the requisite skills for colorectal cancer diagnosis and clinical management. Knowing the signalling mechanisms involved in colorectal cancer targeting will open up fresh possibilities for cancer study in the reader's mind. Researchers and readers interested in finding a cure for colorectal cancer can read this book, according to the authors. The authors, in my view, will be fortunate to have grateful readers who obtain extensive expertise for their current practise in colorectal cancer treatment and therapeutics, as well as for future research.

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PREFACE

Cancer is a disease in which cells develop abnormally and may involve any part of the body. Cancer is distinguished by the sudden development of irregular cells. It spreads to other areas of the body and eventually to other organs; this is referred to as metastasizing. The most common cause of cancer-related death is metastasis. According to a World Health Organization (WHO) survey, about 9.6 million deaths were reported worldwide in 2018, and 7.6 million deaths were estimated in 2008 due to cancer. Lung, breast, colorectal, stomach, and liver cancers are some of the more prevalent cancers diagnosed in men. Breast cancer, colorectal cancer, lung cancer, cervical cancer, and thyroid cancer are some of the more prevalent cancers among women. Changing one's lifestyle and adopting more sustainable habits could prevent about 30 percent of cancer deaths. According to a study released on September 12, 2018 in "A Cancer Journal for Clinicians" by the International Agency for Research on Cancer (IARC), the top three cancer forms are prostate, female breast, and colorectal cancer, both of which are mainly present in humans. Colorectal cancer is the third most commonly diagnosed cancer (1.8 million patients, or 10.2 percent of all cases), followed by prostate cancer (1.3 million cases, or 7.1 percent), and stomach cancer (the fifth most commonly diagnosed cancer) (1.0 million cases, 5.7 percent). Per year, it is projected that 1.2 million people are diagnosed with colorectal cancer.

Colorectal cancer (CRC) is a complex disorder caused by the interaction of hereditary and environmental causes, which can be classified according to the importance of each of these factors. CRCs are often seasonal (70-80%), with age being the most important risk factor; hereditary variants account for just a small percentage of incidents. Colorectal cancer develops as a result of the accumulation of hereditary and epigenetic modifications. The most advanced CRCs grow from adenomas (adenoma-carcinoma sequence). The neoplastic transfer cycle is estimated to be about 10-15 years, which refers to the amount of time required to detect and remove these adenomas before they progress to invasive carcinoma. The three main carcinogenesis pathways for colorectal cancer (CRC) are currently being debated.

This book reflects on the most basic clinical and medical methods for colorectal cancer care. Furthermore, we concentrate on recent advancements in colorectal cancer science as well as the critical mechanisms involved in colorectal cancer treatment.

The chapters of this book are structured in such a manner that even readers with no prior awareness of the topic will learn about it in the book. As a result, the book's contents have been divided into eleven chapters.

We did our best to include relevant knowledge in a clear and concise manner. We hope that by the end of the book, readers will be able to follow other researchers in their pursuit of the topic's estimated supremacy. Furthermore, we hope to be able to contribute to the development of research in this area.

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We would like to convey our heartfelt appreciation to God Almighty for always being gracious and supportive to us. He offered us the chance to thrive and immerse ourselves in His unique molecular universe, which are gifts that only a few humans have seen. We humbly express our gratitude to our families for their patience and generosity throughout the writing of this novel. We would like to extend our heartfelt thanks to all those people who helped us along the way. This book is for those who want to expand their expertise in the area of cancer and keep themselves up to date.

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CHAPTER 1

Colorectal Cancer Diagnosis

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Abstract: A diagnosis is an important tool in the detection and combat of colorectal cancer. Early-diagnosed cancer can be cured easily. There are many invasive as well as non-invasive methods of diagnosis for colorectal cancer. Non-invasive methods usually involve the use of various biomarkers for diagnostic purposes. Recently, enzymes from lysosomes that take part in metastases have been discovered to have importance as a diagnostic tool.

Keywords: Biomarkers, Diagnosis, Invasive, Lysosomal exoglycosides, Non-invasive.

INTRODUCTION

Colorectal cancer is the third leading cause of death from cancer. It is observed that almost 4.3% of men and 4.0% of women in this world is suspectable to have colorectal cancer in upcoming times. The outcome for people with colorectal cancer is improving, but the overall five-year survival rates are still lower than 60%. There is a need for greater accuracy in diagnosis and staging. The astonishing fact about colorectal cancer (CRC) is that among all the colorectal cases, almost half the percentage is reported from developing countries. This might be due to the limited resources for diagnosis and poor health infrastructure, which ultimately leads to increased mortality rates due to CRC. Though, in western countries, the good health infrastructure and early screening and diagnosis improvise CRC treatment. As far as India is concerned, the age standard rate (ASR) for CRC cases is low, approximately 7.2 per 100,000 male population and 5.1 per 100,000 female population; yet India is a nation of 1.38 billion-plus people, with a staggering number of CRC-affected populations, and with a low five-year survival rate (less than 40%) [1].

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Certain epigenetic disorders and genetic alterations can hinder CRC treatment. The basic reason for CRC is the methylation and covalent modification of histones. To make treatment of CRC more effective, early diagnosis of neoplasms and identification of pre-cancerous stageis essential [2]. It hasbeen observed from histological data that CRC can cause perforation within the intestine; therefore, chances of obstructive ileus formation are pragmatic.Most of the patients, who witnessed colonic polyps at early stages, ultimately develops CRC. It is of utmost importance to remove adenomatous polyps to prevent the conversion of CRC from colonic polyps (Fig. (**1**) [3].

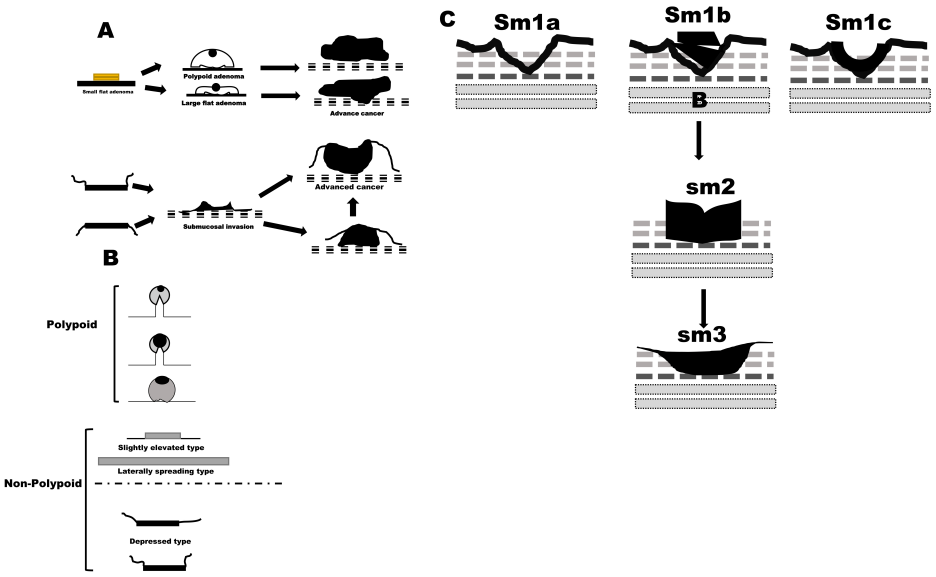

Fig. (1). (A) Developmental process of nonpolypoid colorectal neoplasms; **(B)**. Macroscopic classification of colorectal neoplasms; **(C)**. Submucosal invasion.

Invasive Examination

To identify the CRC, the most common practice is rectal examination. During the examination, almost around 70% rectal and 30% CRCs can be diagnosed. But it is most important to have the necessary experience as a physician who handles the case. Endoscopy is the most prominent tool or method to instantly recognize CRC.

To perform the histological examination and to perfectly identify and localize tumors associated with CRC, it is important to perform sigmoidoscopy and colonoscopy, which are a type of endoscopy [4]. With the help of recent

advancements in endoscopy, it is possible to detect tumors with up to 92-97% accuracy. If there is an advancement of CRC to lower parts of the colon, then sigmoidoscopy can play a pivotal role in diagnosing the condition, whereas colonoscopy helps to inspect the entire colon with the proper illustration of sensitive information. During the diagnosis of CRC, the colonoscopy was found to have many advantages, *viz*., it can increase the accuracy of detection with a limited time frame. To perform the palliative procedure and CRC diagnosis sigmoidoscopy would be a necessary tool. For those patients, who are at potential risk if the surgical operation is performed, sigmoidoscopy can help to clean and identify obstructions generated due to CRC. The biggest disadvantage of sigmoidoscopy is its invasive operations, which can create certain discomfort to the patients; as it may create preformation and bleeding in the intestine [5]. Lead to circumvent such problems, recently developed virtual colonoscopy created a buzz within the scientific community. By applying computer tomography, it is possible to obtain 3D images of the large intestine. Most importantly, the non-invasive virtual colonoscopy helps to decrease the risk of unnecessary bleeding from the intestine [6]. Many imaging tests like nuclear magnetic resonance (NMR), endorectal ultrasonography (USG) help to identify the actual conditions of CRC when the patient has severe focal lesions. From the biomedical research, it was found that, alternation of carbohydrate, fluor-18-fluorodeoxyglucose positron could be the reason for CRC. The positron emission computed tomography (18F-FDG PET/CT) depicts a prognostic value with response to the treatment. The 18F-FDG PET/CT tomography helps to identify the potential chemotherapeutic challenges in patients, who are affected with CRC. From the ongoing research, it was observed that 18F-FDG-PET/CT has a significant amount of CT sensitivity; which allows researchers to identify cancer metastases within the liver. Many pieces of research suggest that positron emission tomography (FDG PET) was found to be the most potent tool to identify the interpreted results from gastrointestinal stromal tumours. The treatment using 18F-FDG-PET/CT has shown positive responses within 10 days of the initialization of treatment. This technique is more effective in patients after radio-chemotherapy. As per the NICE guidelines 27, if the body persists lesion, colonoscopy is recommended.

NON-INVASIVE DIAGNOSIS METHODS

Fecal Occult Blood Test

In this technique, the hemoglobin content was identified in human fecal. If traces of hemoglobin are found, it indicates that the blood might be shedding from polyps (1-2cm) or CRC. This test needs to be repeated several times to enhance sensitivity up to 90%. In CRC diagnosis, the scientist is concerned about the

CHAPTER 2

Screening for Colorectal Carcinoma

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Abstract: Colorectal carcinoma is the fourth most commonly diagnosed malignancy. As it is hidden in many cases and as the onset is undetectable, it may prove to be fatal. Hence, early screening colorectal cancer is a way to prevent this disease. Screening depends upon various factors, such as familial history, history of the disease, or any condition which could lead to colorectal carcinoma. Various tests, such as fecal occult blood test, sigmoidoscopy, and CT scan, are available for screening. The screening method to be used depends upon various contributing factors. Screening can be invasive or can be non-invasive using many markers.

Keywords: Detection, Early diagnosis, Novel tests, Screening tests.

INTRODUCTION

Colorectal carcinoma, the fourth most common internal cancer, is a common internal malignancy. In Canada, around 24,800 new cases of colorectal carcinoma were reported in 2021, and 9600 deaths of affected individuals. The disease occurrence per year has increased in men and women since 1988. In terms of the benefits of detecting colorectal carcinoma, population-based screening is gaining popularity around the world. In January 2007, Colon Cancer Check was introduced by the Ontario Ministry of Health and Long-Term Care and Cancer Care Ontario in a collaborative approach. The probability of having this cancer at birth is 7.4% in men and 6.5% in women, while the probability of dying with this cancer is 3.7% in men and 3.3% in women [1].

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DETECTION OF EARLY COLORECTAL CARCINOMA

The survival of the patient depends on the stage of CRC at which they have been diagnosed. In England, The National Bowel Cancer Screening Programme showed a reduction of colorectal cancer in the early stage detected group than the control group. This helped in understanding that the early-stage detection of the disease could help in the prevention of most colorectal carcinoma [2]. Several colorectal carcinomas do not show any symptoms until a stage where a certain obstruction might result in altered regular bowel habits and may cause abdominal discomfort. Blood in the stool can be seen at the early stage of colon and rectal carcinoma, which is frequent and unpredictable. The disease starts with a crypt and with the progression of gene mutations, further giving rise to small polyp, which then sooner or later metastasizes. This natural process provides a window of time for detection as early as possible and then removing the polyps. With an early-stage detection of carcinoma, the deaths and disease can be reduced drastically [3].

EARLY DIAGNOSIS OF COLORECTAL CARCINOMA

The need for colorectal cancer screening is urgent and widespread and serious, as it was the second leading cause of death in Canada, affecting both men and women equally. Early detection of carcinoma was possible with some screening tests with high accuracy. The early-stage removal of adenomatous polyps helped in the reduction of incidences and also reduced mortality due to colorectal carcinoma. The advantages of early screening compensate for its problems.

Significant efforts are needed from patients, medical practitioners, and government. As in Canada, the low percentage of detection was contrasted with the indicative presentation [4].

WHAT IS SCREENING?

Screening is the identification of potential patients who might likely have colorectal carcinoma or adenomatous polyps without showing any indications or signs. Reducing the mortality rate is the main reason for screening [5].

WHO SHOULD BE SCREENED?

New cases could be seen without any affecting factor for colorectal carcinoma. Occurrence is about 75%. People without any factors are at very low risk compared to the ones who have any family history of colorectal carcinoma, which is about 15 -20%. Hereditary nonpolyposis colon cancer accounts for 4–7% of the total cases, and familial adenomatous polyposis accounting for the remaining 1%.

The remaining 1% consists of a variety of unusual disease situations like Crohn's colitis, Peutz-Jeghers syndrome, chronic ulcerative colitis, and familial polyposis. Various factors that could be kept in mind are low fiber and high saturated fat diet, older age, inactive routine, and extreme consumption of alcohol [6].

Depending on the risk of colorectal cancer the screening is different. With some questions asked, the risk can be defined well for colorectal cancer:

a. Have you ever suffered an adenomatous polyp or colorectal cancer?
b. Is there any history or current medical condition of diseases such as inflammatory bowel disease that could lead to or influence colorectal cancer?
c. Is there a family history of adenomatous polyps or colorectal carcinoma? If yes, then how many members of the family are related to the patient, and at what age was the first polyp detected [7]?

SCREENING PEOPLE AT AN AVERAGE RISK FOR COLORECTAL CARCINOMA

Screening need to be offered to average-risked men and women. Use of fecal occult blood test, colonoscopy, or sigmoidoscopy in adults of age 50 - 75 year is suggested by the U.S. Preventive Services Task Force. Due to a lack of evidence, positive or negative effects of fecal DNA testing and computed tomography colonography as screening modalities for colorectal cancer are not known. Due to the presence of options, patients may choose screening techniques depending on their preferences [8].

Fecal Occult Blood Test

This involves tests based on dietary restriction. Guaiac-based test that has dietary restrictions or the immunochemical test, which has no dietary restriction. Within three consecutive stools, two would be taken for examination without rehydration. Colonoscopy is suggested for patients who might get the test positive. The FOBT screening test has helped reduce the mortality rate in Minnesota trials by 21%. A review of three clinical studies found that a restricted diet cannot reduce the positivity rate in older people and that a very strict diet may reduce compliance and reduce sensitivity to the guaiac-based test [9]. A major drawback of this test is that it cannot detect some carcinoma and polyps. False test results could have been seen for colorectal neoplasia, and due to this, the patient might need to go through cost, risk, and discomfort of colonoscopy without much advantage [10].

CHAPTER 3

Histopathology

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Abstract: Histopathology involves the study of tissue samples using a microscope to understand the normal and abnormal contents of a given sample. Normal histology of colorectal areas, such as mucosa and muscular, is greatly altered during the development of cancer. Colorectal cancer can be divided into various grades during the histopathological examination of tissues, which shows the extent of invasion of tumour into the colon. This examination can also be used to understand the type of carcinoma in the colon. Many factors affect this histopathological study and many drawbacks can occur in grading systems that need to be improved.

Keywords: Alterations, Grading, Histopathology, Normal histology, Variant.

INTRODUCTION

Histopathology involves scanning of tissue samples under the microscope to investigate and understand the presentation of disease at a cellular level. It allows us to understand any cellular abnormality which occurs in the disease. This feature can be used to identify the grade of cancer, showing the extent of growth/spread of cancer. The variant of cancer has its characteristic appearance in a microscopic examination which can be easily identified and treated accordingly. Grading can be done by various methods, however, they have their drawbacks.

NORMAL HISTOLOGY OF COLORECTAL AREA

The colon has a mucosa made of columnar epithelium. It shows the presence of a brush border. Many goblet cells secreting mucus are present in this layer. Lamina propia is rich in leukocytes and lymphoid modules buried into the lower layer. Muscularis mucosae are prominent and can be divided into an inner circular layer and outer layer arranged lengthwise. The submucosa is a mixture of irregular con-

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nective and adipose tissue. It contains many blood vessels and neurons. Muscularis externa is made up of thick bands of muscles running along the length of the colon [1].

The rectal region shows histology more or less similar to the colon. Classic features, such as teniae coli and haustra, are absent in the rectal region. The muscular layer is well-developed, which helps in contraction during defecation [2].

GENERAL PRESENTATION IN COLORECTAL CANCER

In the first stage (stage 0) of colorectal cancer, dysplasia of epithelium of the colorectal area causes abnormal growth, leading to the formation of a mass of cells or polyps. Due to genetic abnormalities, the cells in polyps now divide uncontrollably to form neoplasia. These neoplastic tumors are localized to the epithelium or endothelium. They do not exhibit potential for metastasis.

The extensive dysplasia in the localized tumour is associated with some rather distinguishable changes in cell structure and architecture. Changes in architecture can be as remarkable as seeing glandular epithelial cells in the muscularis of the colon. Cells and nuclei can be seen in more than one distinct shape. The amount of chromosomal material in the nucleus is more than normal. The polarity of a nucleus is disturbed due to cytoskeletal disturbances. The nuclei may exhibit crowding. Cells, due to genetic abnormalities, lose their glandular structure. The nuclear matter is in excess and can be seen arranged irregularly.

High-grade dysplasia in polyps is also accompanied by many changes in the cellular structure. The cells in the polyp may lose their glandular nature; the mucin production may stop permanently; the nuclear matter is in a higher amount as compared to cytoplasm; the appearance of nuclei also changes; and The cells may appear irregularly arranged in cribriform shape.

In the second stage (stage 1), cancer spreads to the layer below the mucous membrane, *i.e.*, to the submucosa. This certifies the polyp being cancerous. This tumour now has the ability to enter deeper into the layers of the intestine and invade the vasculature of the body [3].

In further stages, the polyp invades deeper into layers of the colon, finally crossing muscularis mucosae to enter the lymph nodes through which it can travel to other organs.

NEED FOR HISTOPATHOLOGICAL INSPECTION IN COLORECTAL CARCINOMA

1. Histological variants- there are many variations that can be seen in manifestations of colorectal carcinoma, such as mucinous adenocarcinoma, signet ring adenocarcinoma. These have different histologic features which can be diagnosed through histopathological studies. These help to identify variants, such as medullary carcinoma involving sheets of cells with a round nucleus with growth along the circumference of the tumour [4].
2. Cancer staging- earlier staging of colorectal carcinoma is based on gland formation in the tumour. But this analysis is not accurate due to high variability in individuals regarding gland formation. And the behavior of tumours, whether differentiated or not, is not very much different. Hence, a new criterion for dividing tumours into stages based on poorly differentiated clusters (PDC) is employed where the number of PDC is used to differentiate cancer into stages where the greater number of PDC means more advanced stage [5].
3. Prognosis- histopathological analysis can help to predict any future manifestations of colorectal carcinoma. Histopathologic analysis can reveal many parameters of the tumors, such as the variant, tumour stage, and invasion depth [4].

FACTORS INVOLVED IN THE HISTOPATHOLOGICAL ANALYSIS OF COLORECTAL CARCINOMA

1. Tumour grading- tumour grading is an important method for the prediction of prognosis and identification of tumours. But there is more than one way of grading the tumours, and they are not similar at all.
2. Nuclear grading- it involves analysis of size and shape of nucleus of dividing cells and implies that lower grade cancers do have very few numbers of such cells.
3. Tumour budding- it involves the formation of undifferentiated cells near the invasive edge of the tumor. The extent of budding affects the probability of recurrence even after the treatment. These ‘buds’ are very small in size and do not have any special function, such as secretion of mucin. Hence, distinguishing these buds from colorectal carcinoma is pretty difficult.
4. Tumour border architecture- it can be either smooth or rough. It does not indicate any staging of the tumour, but itself is an indication of worsening the condition of malignancy. Budding is observed more frequently in tumours with an irregular border [6].

CHAPTER 4

Chemotherapy and Colorectal Cancer

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Abstract: Chemotherapy is one of the established first-line options for the treatment of colorectal cancer. Chemotherapy contains various molecules acting against multiple factors, contributing to the growth of cancer cells. Chemotherapeutic regimens can vary based on the stages of cancer and the components as well as the strength of medications. The recent addition of agents such as antibodies against various molecular targets involved, such as receptors and components of signaling pathways, resulted in even more precise therapy.

Keywords: Chemotherapy, Components, Novel agents, Stages of cancer, Targeted therapies.

INTRODUCTION

Chemotherapy is the use of chemical moieties to treat cancer. Chemotherapy can be given systemically as well as locally. Chemotherapy regimens change based upon the cancer stage and include components having varied mechanisms of action. Their combinations show a synergistic effect in killing the cancer cells.

CHEMOTHERAPY AND COLORECTAL CANCER

Chemotherapy involves the treatment of colorectal cancer using medications that are taken orally or through an I.V. The drugs travel throughout the body and reach the desired tumour site, where they show their effect and kill the cancer cells [1].

Administration of Chemotherapeutic Agents

Systemic chemotherapy involves the entry of drugs and delivery through the bloodstream to reach the position of cancer in the colon or rectum. The drugs

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involved in systemic chemotherapy are fluorouracil, capecitabine, irinotecan, oxaliplatin, trifluridine, and tripiracil (American Cancer Society) [1].

Regional chemotherapy: This type of therapy is carried out for metastatic cancers which may have spread to the liver. The hepatic artery, the most anticipated route of metastasis, is targeted. The artery is blocked to cut blood supply to the liver. Then drugs are injected, which enter the liver and show their effect limited to the liver only [2].

CHEMOTHERAPY IN DIFFERENT STAGES OF COLORECTAL CANCER

Chemotherapy is administered based on the stage of cancer, which describe its severity and progress. It is divided into stages 0 to 4 depending on the severity and progress. Stage 0 cancer is limited to layers of the colon and rectum. Surgery to remove the cancer is the most frequently sought option to get rid of cancer. Surgery includes the removal of a locally formed polyp or tumor. But in the case of large tumours, the area of the colon should be removed. Stage 1 cancer invades deeply in the colon but not outside of it. If the cancer is a part of polyp, it can be removed, and no cells are present at the edge. If the polyp is high grade, deeper surgical intervention is required. For cancer not in a polyp, the colon section must be severed [3].

Stage 2 cancers can be classified according to the level of invasion into their surroundings. 2A stage involves cancer reaching to tissues around the colon. 2B cancers reach as deep as the peritoneum and 2C cancers cross the peritoneum and reach even other organs. For this type of cancer, surgery for the removal of a specific part of the colon is the main method and adjuvant chemotherapy is also used to shrink the tumors. National comprehensive cancer network (NCCN) gives guidelines that vary upon high-risk factors, poorly differentiated clusters, invasion in lymph and other organs. For the 2A stage, treatment with 5-fluorouracil, leucovorin, or capecitabine is suggested. For those who exhibit high-risk factors in stage 2A or have progressed to stages 2B and 2C, treatment includes a combination of 5-fluorouracil & leucovorin, capecitabine, or a combination of 5-fluorouracil, leucovorin, capecitabine or therapy, including 5-fluorouracil, leucovorin, oxaliplatin, or a combination of oxaliplatin & capecitabine. In this treatment, the risk and benefit should always be considered [4].

Stage 3 cancers completely cross various layers of the colon and may invade nearby tissues by reaching nearby lymph nodes. Surgery is still the first option, and adjuvant chemotherapy is given to shrink the tumour. The chemotherapeutic regimen should start after a duration of 8 weeks from surgery and should last 5-6 months after surgery. The first-ever combination given was 5-fluorouracil and L-

folinic acid daily for 5 days in a month. After the addition of capecitabine in this regimen, the new combination showed a better effect and tolerance than the earlier combination. The addition of oxiplatin to 5-fluorouracil, folinic acid, and capecitabine enhanced the overall as well as the disease-free survival rate above 70% as compared to only fluoropyrimidine. Combinations such as FOLFIRI (folinic acid, fluorouracil, irinotecan), IFL(irinotecan & fluorouracil), and FOLFOX (Fluorouracil, oxaliplatin & folinic acid) are used in metastatic cancers, but these combined with VGEF/EGFR targeted therapies did not show any significant effect. The validated regimen for stage 3 includes combinations such as FOLFOX and CAPOX as a doublet regimen and combinations such as LV5FU2 (leucovorin & 5-fluorouracil) and capecitabine without oxaliplatin. CAPOX is superior to FOLFOX, where the number of injections is less. Dipyrimidine dehydrogenase deficiency should be considered before any treatment to avoid the toxicity of capecitabine (Adjuvant Chemotherapy for Stage III Colon Cancer, Julien Taieb 1,2,* and Claire Gallois 1,2).

Stage 4 cancers involve the spread of cancer to distant tissues. Chemotherapy is the major treatment option to control the spread of cancer. Surgery is not always preferred but can be considered for patients showing metastasis. 5-fluorouracil was the most preferred single-molecule for the treatment of progression of colorectal carcinoma. The addition of leucovorin as a biomodulator enhances the response and this combination is the best choice for patients intolerant for chemotherapy. Mayo and Rosewell park regimens of this combination are widely used. This combination shows better response and progress-free survival. Capecitabine, a fluorouracil prodrug can also be used along with leucovorin which reduces the toxicity even further.

Irinotecan is used solely when the above combination fails and has been shown to prolong survival by 2-3 months. In combination with 5-fluorouracil and leucovorin, it showed an even greater survival benefit. Irinotecan given along with i.v. bolus fluorouracil improved the survival time to 17-20 months. When combined with capecitabine, it showed increased toxicity; hence, it is not applied anymore. Oxiplatin, when used alone, has shown limited efficacy. When it is coupled with fluorouracil, leucovorin as a FOLFOX combination shows a much greater benefit. Along with capecitabine as a CAPOX combination, it can be used as first as well second-line therapy [5].

COMPONENTS OF CHEMOTHERAPY

5-Fluorouracil (5-FU)

5-FU is commonly used in patients with advanced-stage colorectal carcinoma. It is a member of the fluoropyrimidine class. This molecule incorporate itself into

CHAPTER 5

Robotics for Rectal Cancer

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Abstract: Surgery is one of the primary methods for the removal of colorectal cancers. Various surgeries are performed based on the location of cancer and its spread. Due to many shortcomings of extensively invasive procedures, laparoscopy was invented to visualize cancer perfectly and later remove that tumor. However, some technical difficulties were observed, and the physiological complexity of the tumour site caused this method to fail. Later, the FDA announced the approval of a surgical system operated by a team of specialists. This system has more enhanced precision compared to conventional treatments, showing increased efficacy.

Keywords: Efficacy, Laparoscopy, Local excision, Side effects, Surgical system, TME.

INTRODUCTION

Along with chemo and radiotherapy, surgery is another effective treatment for the removal of colorectal cancer. Surgeries are useful in removing tumors that have invaded into deeper layers or, if detected early, can even completely remove the malignancy. Surgical techniques improved with time to give more efficacy and reduced incision size as larger incisions are associated with greater discomfort. This chapter shows such evolution of surgical systems for the treatment of colorectal cancer.

There are many options for surgical removal of rectal cancers.

TOTAL MESORECTAL EXCISION

TME is a broad term used for surgeries to remove rectal cancer. The procedure involves removal of mesentery near as well as far away from the tumour. It is removed sharply while taking care of the autonomic neural network in the area,

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maintaining hemostasis, and the integrity of the mesorectal envelope. It is carried out under the rationale that maximum spread of rectal cancer is not beyond mesentery, and removal of mesentery may help prevent the spread further [1].

Techniques Abdominoperineal Resection

Abdominoperineal Resection involves a midline incision through which the abdominal cavity can be accessed. The lymph nodes in the area are examined to assess the spread of tumours. In ureter, gonadal vessels are pushed upwards, and colon and mesocolon are pulled down. The arteries and bowels are ligated while taking care not to harm any organ during that process. Then the mesentery is dissected, starting from the sides and coming to the middle part of the mesentery. Nerves are pushed to the side. Next, the position of the perineum is ensured. The rectum is cleaned, the anus is closed tightly, and an elliptical cut is given around the anus. The ligaments present before the coccyx are divided and the surgeon, with his finger, pulls down the perineum. The excision starts at the backside, comes to the front from the sides. After the removal of cancer, the ligatures on blood vessels are removed and the layers are sewn [2].

Coloanal Anastomosis

This procedure is important for tumors that are present near the sphincter. This procedure enables a surgeon to successfully remove a tumor without harming the sphincter. This is done for the patient suffering from rectal cancer, which is a distal position and has not yet invaded muscular layers of the sphincter and for whom, anterior resection is not possible. The rectum is cut at a distal angle near the pelvic muscles. The remaining muscles are removed and the diseased area is removed. The ends are sewn to restore connectivity [3].

LOCAL EXCISION

Low anterior resection and abdominal perineal resection are majorly used for the removal of rectal cancers, but they usually come with many risks, such as high mortality and morbidity. Hence, the method for local excision to remove the tumour is gaining an advantage [4].

Transanal Excision

For cancers present lower side, local excision is made transverse to the anus. After anesthesia, the patient is made to sleep on his/her stomach. The buttocks are pushed apart. Pudendal nerves are blocked to reduce pain. A retractor is used to expose the lesion inside the anus. Sutures are placed 1-2 cm away from a tumour and a line marking the dissection site is drawn. The tissues are cut using

electrocautery. The lesion is cut while taking care not to harm the other structures. After removal, the excision is filled with polyglycolic structures and sealed [5].

Transcoccygeal Excision

This approach is used for lesions in the middle or distal portion of the rectum. The patient is administered general anaesthesia and made to lie in a prone position. The buttocks are kept apart for the comfort of the surgeon. The patient is draped and sterilized using iodine solution. A cut is made in the posterior along the middle line near the coccyx and sacrum. As the coccyx lies near to the skin, to reach it, the layers such as ligaments are cut from the side and posterior end of the coccyx. The coccyx is pushed to the side and cut from the anterior side till cauterizing wire passes through a sacral coccygeal joint. The coccyx is removed and any bleeding from the sacral artery is controlled using electrocauterizing. Levitator muscles and a fat layer are moved to reach the rectum [6].

For posterior tumors, the distal portion of tumour can be felt using fingers. After that, the rectum and mesorectum are cut transversally by 1-1.5 cm away from the tumour. For posterior tumours, this method allows the removal of perirectal nodes. For lesions in the front side, the rectum is cut from the posterior side, and the lesion is exposed clearly. The perianal fat along with the lesion is separated by a radius of 1-1.5 cm around the lesion [6].

Transsphincteric Excision

It involves dissection of the sphincter as well as posterior rectal wall. It is similar to transcoccygeal excision except that now the levator ani and sphincter muscles are divided along the midline. These muscles are re-positioned carefully so they can be sewn back at the end of the procedure. Care has to be taken to not damage the nerve supply to the anus and rectum. After the removal of the lesion, the layers are sewn back again [7].

Transanal Endoscopic Microsurgery

This procedure is performed with the help of a special rectoscope. An obturator was placed before the insertion of a microscope. A glass faceplate is used to hold the position for the insertion of a microscope. The scope is inserted and the glass plate is removed. Carbon dioxide is blown into the rectum to distend it. Epinephrine is injected to allow hemostasis. The margin of resection of 1-1.5cm around the lesion is marked and resected along with the fat layer present around the rectum. The wound is sewn using absorbable sutures [8].

CHAPTER 6

lncRNA NLIPMT Inhibitors in Colorectal Cancer Management

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Abstract: Colorectal cancer (CRC) is a disease that is initiated by the interrelation of genetic and environmental factors. Colorectal cancer progresses through the accumulation of genetic and epigenetic changes. This review discusses, in detail, the role of lncRNAs in colorectal cancer, focusing on various signaling pathways involved in colorectal cancer pathogenesis, *viz*., Wnt/-catenin signaling pathway, epidermal growth factor receptor (EGFR)/insulin-like growth factor type I receptor (IGF-IR) signaling pathway (KRAS and phosphatidylinositol-3-kinase (PI3K) pathways), transforming growth factor-beta (TGF-) signaling pathway, p53 signaling pathway, and the epithelial-mesenchymal transition (EMT) program.

Keywords: Apoptosis, Colorectal cancer, LncRNAs, Signalling pathway.

INTRODUCTION

Cancer is the abnormal growth of cells that can affect any portion of the body. The rapid formation of abnormal cells is the defining feature of cancer, and then it enters adjoining parts of the body and escalates to other organs; the last process is stated as metastasizing [1]. Cancer metastases are the leading cause of death [2]. According to the report of the World Health Organization (WHO), in 2018, around 9.6 million deaths were estimated worldwide, and 7.6 million deaths were estimated in 2008 from cancer [3]. Some common types of cancer found in males are lung, prostate, colorectal stomach, and liver cancer [4]. Breast cancer, colorectal cancer, lung cancer, cervical cancer, and thyroid cancer are some of the most common types of cancer in women [5]. Changing one's lifestyle and adopting healthier habits could prevent nearly 30% of cancer deaths [6]. Based on

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the report of the International Agency for Research on Cancer (IARC) published on September 12th, 2018 in "A Cancer Journal for Clinicians," it has been shown that the top three types of cancer found in human are lung [7], female breast, and colorectal (Table **1**).

Table 1. lncRNAs in the blood of cancer patients have been found to circulate.

lncRNA	Associated Cancer
RP11-04K16.1, LOC_012542, PVT1	Cervical Cancer
SNHG1, RMRP	Lung
H19	Multiple myeloma
PCA3, BCAR4, CRNDE-h,	Colorectal
LNCV6_116109, LNCV6_98390,	Gastric
LNCV6_38772, LNCV_108266,	Hepatocellular
LNCV6_84003, LNCV6_98602, u50535	carcinoma
H19, lncUEGC1	
LINC00161	

Cancers of the lung and breast account for the majority of cases globally; in 2018, an estimated 2.1 million people were diagnosed with these diseases. Second, in terms of several instances, colorectal cancer has 1.8 million cases and is 10.2% of all cancers diagnosed; prostate has 1.3 million cases and is 7.1%; and stomach cancer is fifth in terms of the number of cases (1.0 million cases, 5.7 percent) [7]. It has been estimated that around 1.2 million patients are diagnosed every year with colorectal cancer [8] (Hermann Brenner *et al.*).

As a multifactorial illness, colorectal cancer (CRC) may be divided into several subtypes based on the relative weight given to each of these risk factors [9]. Only a very small percentage of CRCs are caused by hereditary types of the disease, which accounts for 70% to 80% of cases (Binefa G *et al.* Colorectal cancer prevention and treatment) [10]. The accumulation of genetic and epigenetic alterations is how colorectal cancer grows (Fig. (**1**)). Adenoma-carcinoma transition period is around 10-15 years, which indicates the time available to discover and remove these adenomas before they become invasive carcinomas [11]. Carcinogenesis of colorectal cancer (CRC) is now being debated in three primary ways [12].

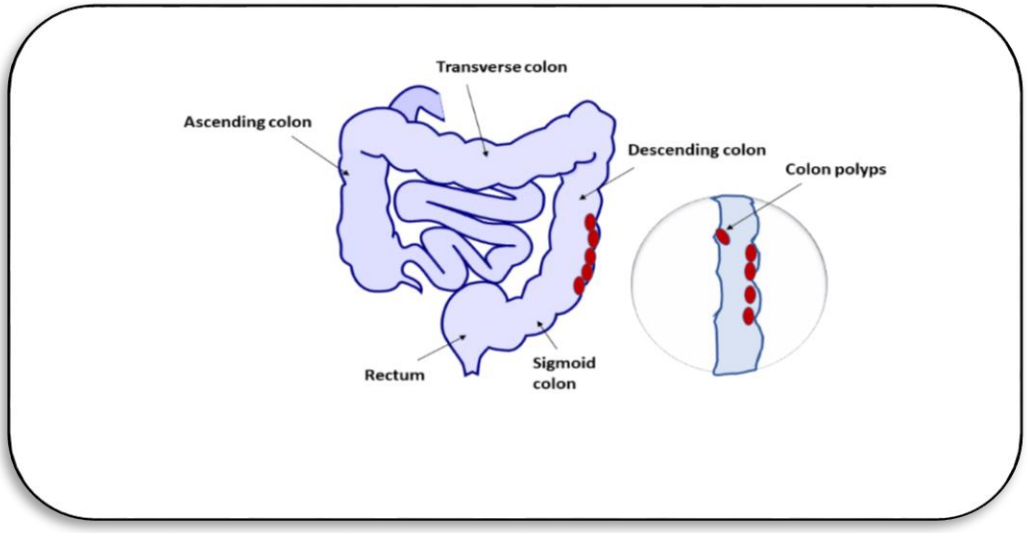

Fig. 1. Onset of Colorectal Cancer.

The first route is known as the "pathway of chromosomal instability" [13]. This path involves the accumulation of mutations that activate oncogenes (KRAS) and inactivate suppressor genes (DCC, APC, SMAD4, TP53) [14]. DNA replication mistakes accumulate owing to mutations in genes that are responsible for correcting them (MSH 2,6,3, MLH 1,3, PMS 1,2, and Exo1) [15] and third route known as "aberrant hypermethylation, a mechanism to silence gene function". The CpG island methylator phenotype (CIMP) refers to dinucleotide methylation in numerous gene promoter regions [16]. The CIMP accounts for 15%-20% of sporadic CRC [17]. CACNA1G, IGF2, NEUROG1, RUNX3, and SOCS1 are all considered CIMP-positive indicators if they are methylated [18]. Nearly two-thirds (60%) of all instances of colon cancer occur in industrialized nations, with the highest incidence in Japan. In part, this low death rate can be attributed to the implementation of a screening programme in 1992 [19] (Table **2**), one of the first in the world, along with Italy and Israel. CRC is the third most common disease in Europe and is the main cause of deaths due to cancer in the country [20].

Table 2. Colorectal cancer screening programs across the world have a variety of characteristics. FOBT: Fecal occult blood test; FS: Flexible Sigmoidoscopy; CS: Colonoscopy.

Country	Test	Periodicity	Target Population (age)	Year
Germany	FOBT FOBT or CS	Annual Biennial/Every 10yr	50-54 ≥ 55	1971
Italy	FOBT FS	Biennial Once-only	50-69/74 58-60	1982

CHAPTER 7

Pathways in Colorectal Cancer

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Abstract: Signaling pathways are important tools for regulating cellular life cycles such as growth and replication. Any external influences may cause a disturbance in signaling, causing an uncontrolled division of cells causing cancer. Many receptors such as EGFR are active in signaling for cancer, which can be targeted to show potent anticancer activity.

Keywords: Chromosomal instability, Microsatellite instability, Pathways, Signalling.

INTRODUCTION

Signaling pathways are important in long-term cellular activities such as the growth and development of cells. Many hormones are involved in such growth, which regulates the various intracellular process. Any disturbances in these pathways may cause disturbances in related processes, which may lead to malignancies [1].

Colorectal cancer is the third most commonly found cancer in men and the second most common cancer in women. It is caused by various genetic and epigenetic alterations, which cause the generation of tumours in colorectal cancer. A four-step pathway is suggested by scientists to explain the generation and progression of colorectal carcinoma.

Three principle genetic abnormalities involved in colorectal carcinoma are:

CHROMOSOMAL INSTABILITY PATHWAY

This pathway is also called as adenoma-carcinoma progression pathway. Its progression into the evolution of disease can be easily predicted and shows

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specific histology. This pathway causes a proto-oncogene K-Ras and inactivates three suppressor genes, namely loss of APC, loss of p53, and loss of heterozygosity for the long arm of chromosome 18 [2].

Adenomatous Polyposis Coli gene and wnt Signaling Pathway

APC gene-associated polyposis includes conditions such as familial adenomatous polyposis, attenuated FAP, Gardner, as well as Turcot syndrome. FAP gene causes the development of many pre-cancerous polyps around the age of 20. The polyps may turn into a carcinoma decade later. Attenuated FAP shows fewer polyps, and cancer develops later. Gardner syndrome is associated with soft tissue tumours and osteoma, and Turcot syndrome cause nervous system tumours. APC prevents entry of cell into S-phase from G1- phase. The stem cells do not differentiate and remain in the crypt, which allows them to survive. B-Catenin is important in the Wnt signaling pathway and is degraded by the regular APC gene, hence preventing the survival of cancer cells. In sporadic CRC with wild-type APC gene, hypermethylation or point mutation in promoter region causes the continuation of Wnt pathway. Normally, epithelial cells are shed within a week, but such a mutation causes changes in phenotype and prevents shedding of cells, leading to accumulation. This causes the formation of polyps [3].

TP-53 Mutation

TP-53 gene controls cell cycle and apoptosis and usually undergoes mutations in CRC. P53 protein causes the cell cycle to stop and repairs DNA before replication. If the DNA is not successfully repaired, it causes apoptosis of cells. Inherited or germline mutations in tp53 cause a variety of syndromes such as Li-Fraumeni syndrome, affecting various systems such as neurons and soft tissues [4].

18q Loss of Heterozygosity (LOH)

LOH is the loss of one or both the alleles of a gene. This LOH in 18q is frequently seen in advanced colorectal cancer. The remaining allele is also mutated. This missing part contains DCC (Deleted in Colorectal Cancer) gene coding for a similar protein which prevents cell division even in the absence of a ligand. Cells deep in crypts of the colon produce netrin-1 which then declines due to binding to the DCC receptor. This decreasing netrin-1 concentration is essential for the apoptosis of cells. When the DCC gene undergoes mutation, due to the absence of the DCC receptor, the netrin-1 gradient does not reduce and apoptosis is arrested causing continuous growth. Netrin-1 can be overexpressed which resists the apoptosis by DCC [5].

MICROSATELLITE INSTABILITY PATHWAY

DNA nucleotides may be altered by environmental mutagens and errors. During replication, the DNA polymerase enzyme 'reads' one strand to attach the complementary base pairs. But the DNA polymerase enzyme is not always accurate and errors can happen. As the enzyme reads in a 5' to 3' direction, it keeps checking back for errors. If any mistake is found, the enzyme moves back to the position, uses its ability to cleave that base. This function does not always give accurate results. Hence, another system, the mismatch repair system checks and corrects the pairing. Microsatellite instability is seen majorly in Lynch syndrome characterized by an increased probability of cancers of linings such as epithelium, endometrium, skin, brain.

Short tandem repeats (STRs)/microsatellites are small DNA segments containing mono-, di-, tri-, and tetra-nucleotides repeated hundreds of times. These are frequently found in humans. The STRs found in humans are mostly dinucleotide repeats. The microsatellites are alleles in genomes always present in two copies. During replication, a stutter in enzyme may occur which is seen more in the area of these microsatellites. MMR enzymes try to correct this phenomenon by proofreading the microsatellites which preserve the genetic integrity of the human genome. A defective MMR system will leave the genome with shorter or longer microsatellites, which is called microsatellite instability. Inactivation of MMR enzyme may happen due to sudden methylation of promoter gene or point mutations at MMR family. Microsatellite high (MSI-H) is a condition of instability in more than 30% of the markers. Patients with a minor loss of MMR capacity may develop CRC later till the age of 40. I sporadic CRC, the majority of defects are due to hypermethylation of promoters which prevent their expression. As both the alleles are not lost, the MMR function is present but it is chaotic.

MSI tumours are generally seen at the proximal side of the colon and show a cellular structure similar to mucinous carcinoma. It also shows WBC infiltration similar to Crohn's disease [6, 7].

MMR system is effective in correcting the effect of some chemotherapeutic agents, hence granting chemoresistance to malignant cells. MMR also recognizes complexes made in DNA by drugs such as cisplatin, oxiplatin, and 5-fluorouracil hence even after treatment, the prognosis is not altered.

EPIGENETIC INSTABILITY AND CPG METHYLATION

Many mechanisms are responsible for the regulation of DNA expression without a change in nucleotide sequence. Mutations in the promoter region due to sudden methylation may cause changes in epigenetic regulation. Many a time, patients

CHAPTER 8

Radiotherapy in Colorectal Cancer

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Abstract: Radiotherapy has become an integral part of the treatment of colorectal cancer. Radiotherapy is used as adjuvant therapy in combination with chemotherapy or surgery. In the article, various types of radiotherapy are explained and also the factors involved in the selection of radiotherapy. There have been many clinical trials for investigating the efficacy of various novel radiotherapies, which may show some promising results. Radiotherapy can be adjuvant or neoadjuvant in the combination of first-line therapy to increase the overall effectiveness of the treatment

Keywords: Colon, Radiotherapy, Rectum.

INTRODUCTION

As per the data, in 2018, about 1.7-1.9 billion people have been diagnosed with colorectal cancer, and the deaths reported are close to 900000 [1]. Colorectal cancer is considered one of the common forms of cancer worldwide, with some reports suggesting it as the third most commonly occurring cancer. The most affected countries include Australia, North America, European counties, and New Zealand. Generally, for colorectal cancer, a combination therapy approach is employed, which may include chemotherapy, surgery, and radiotherapy [2]. Radiotherapy is the mainstay of the treatment, whereas chemotherapy and surgery can be used in combination. Radiotherapy, as the name suggests, is a radiation treatment that generally uses higher doses of radiation to kill tumor cells and then shrink them. Also, at lower doses, these radiations are used in X-rays as a diagnostic tool to look inside the body [3]. At higher doses, these radiations kill tumour cells or slow down the progression of a tumour by damaging the DNA. So, when these tumour cells are damaged, the phenomenon is irreversible and becomes non-repairable. When these damaged cells undergo apoptosis, they are discarded by the body. Radiotherapy is not an immediate process and cell death

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takes more time. Generally, days to weeks are needed after the DNA is damaged to total cell death. The cell death process then continues as radiation therapy is continued [4].

TYPES OF RADIATION THERAPY

Radiation therapy can be classified into two types which is:

External beam radiotherapy (EBRT) and

Internal radiotherapy (brachytherapy) [5]

The choice of radiation therapy is based on many of the factors, and some of the factors are listed below:

- The type of cancer
- The relative size of the tumour
- Actual location of the tumour
- Medical history and overall health of a patient
- Contraindication and allergy scenario
- Other factors like age, gender, patient preference

The role of radiation pharmacotherapy in locally advanced rectal cancers has been steadily changed over the last 3 decades. It emerged in the '80s with a prevalent adjuvant function due to its ability to decrease pelvic recurrence after surgical resection and increase survival rates in combination with 5-FU-based chemotherapy [6]. In the early 1990s, radiotherapy was questioned, with the induction of total mesorectal excision (TME) that significantly reduced locoregional recurrence (LRR) [7]. Several randomized short-term studies (5 Gy X 5 days) have shown the significance of preoperative radiation therapy plus TME in reducing LRR in patients with stage II and III rectal cancer [8]. According to the American Cancer Society, treating colorectal cancer with chemotherapy and radiotherapy simultaneously could make the radiation therapy work better, and when both these treatment strategies are combined, it is called chemoradiation [9].

Radiotherapy is not commonly used to treat colon cancer, but instead, it is used as an adjuvant with other treatment therapies like before surgery along with chemotherapy, after surgery to fully eradicate the tumour if any of the tumour is left or the surgeon is not sure. If a person is not healthy enough for surgery, radiotherapy can be used in combination with chemotherapy. But conversely, radiation therapy is more commonly used in rectal cancers with or without combination [10].

As stated earlier, there are two types of radiotherapies – EBRT and brachytherapy and both these strategies could be used in treating colon and rectal cancer. The type of radiation therapy most commonly used by people with colon or rectal cancer is EBRT. From a computer-based machine outside the body, the radiation is concentrated on cancer. It is a lot like having an x-ray, but this radiation is more powerful. How often and how long a person receives radiation treatment depends on the reason for the radiation and other variables being given. The treatment may last from a few days to a few weeks [11]. New EBRT methods have been shown to help doctors treat colorectal cancers that have spread to the lungs or liver more effectively while minimizing radiation exposure to surrounding healthy tissues, such as three-dimensional conformal radiation therapy (3D-CRT), strength modulated radiation therapy (IMRT), and stereotactic body radiation therapy (SBRT) [12]. All these methods are used only if the number of tumours is very less and where surgery is not possible. Internal radiation therapy is not used commonly as EBRT but it might be used to treat some rectal cancer. Although, it is not used commonly more research is needed in this area. A radioactive source is inserted inside your rectum next to or into the tumour in internal radiotherapy. This helps the radiation to enter the rectum without going through the belly (abdomen) skin and other tissues, so it is less likely to damage surrounding tissues [13].

CLINICAL TRIALS OR RESEARCH STUDIES OF RADIATION AND CHEMO-RADIATION THERAPY IN COLORECTAL CANCER

Sr.no	Name of the Study	Clinical Conditions	Drug Used and Type of Radiation Therapy	Outcome	References
1.	AMP-224, a PD-1 Inhibitor, With Stereotactic Body Radiation Therapy in Metastatic Colorectal Cancer	Colorectal cancer, Colorectal Neoplasms, Colorectal Carcinoma	Dug used – AMP-224 & Cyclophosphamide. Radiation– Stereotactic body radiation therapy.	Combination of AMP-224 and low dose cyclophosphamide with stereotactic body radiation therapy (SBRT) was well tolerated but no clinical significance was found in metastatic colorectal cancer patients.	[14]

CHAPTER 9

Surveillance for Colorectal Cancer

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Abstract: The incidence of colorectal cancer is very high, and emphasizing the mortality rate of CRC, good screening and surveillance methods are essential for the effective treatment of cancer. Early detection of the CRC is the key for its treatment. If not detected early, it can cause serious symptoms like bleeding and difficulty in bowel movement, which are considered serious symptoms. Different screening procedures are available for the screening and detection of cancer, but the most commonly used technique is colonoscopy, and another less common technique is flexible sigmoidoscopy. People who have a screening colonoscopy have a cancer mortality rate of 68 percent to 88 percent lower. Flexible sigmoidoscopy, although used in many cases has certain limitations, and therefore, colonoscopy outplays it.

Keywords: Colonoscopy, Flexible sigmoidoscopy, Surveillance.

INTRODUCTION

The third most common non-skin cancer is colorectal cancer, affecting men and women of all ethnic groups [1]. Every year, around 150,000 individuals are diagnosed with colorectal cancer, and more than 50,000 die; the lifetime risk is 1 in 23 (4.4%) for men and 1 in 25 (4.1%) for women. When there is a personal or family history of colorectal cancer, an increased risk of developing colorectal cancer is present. One's risk of developing colorectal cancer is often increased by a personal history of breast, uterine, or ovarian cancer. In its early phases, colorectal cancer rarely causes symptoms [2]. Colon cancer typically begins as a harmless or benign polyp. Polyps in the colon may be cancerous or non-cancerous. Screening tests can detect polyps, which can then be removed, preventing the development of colorectal cancer. In up to 90% of cases, early cancers can be healed with surgery. Typically, when colorectal cancer causes bleeding, changes in bowel behavior, or abdominal pain, it progress to a more advanced stage, where less than 50% of patients are healed [3].

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There are several screening options to consider for physicians and patients today, including colonoscopy, flexible sigmoidoscopy, CT colonography (CTC), and stool tests. Other non-general screening tests are also performed, which include virtual colonoscopy and an enema x-ray test. After inserting air in the colon, a virtual colonoscopy is done *via* a CT scan. Air-filled colon images are transformed into images that look like a colonoscopy. If anomalies are detected, a colonoscopy is required. In patients that have an incomplete colonoscopy, it is also helpful. An air-contrast barium enema is an x-ray procedure that involves filling the colon with air and dye to expose the lining. It is often used only if it is not possible to do a full colonoscopy [4].

In addition to expanded screening efforts, recent studies illustrate promising reductions in CRC incidence and mortality. Since gastroenterologists are the predominant and most efficient providers of colonoscopy in the United States, colonoscopy is both the dominant existing form of screening and an important element in the chain of events that leads to adenoma and cancer diagnosis and resection when other screening modality results are positive. In recent years, studies have shed light on the efficacy of CRC screening modalities and addressed long-standing concerns while also igniting new debates [5].

COLONOSCOPY

Since the 1990s, colonoscopy has become the most popular CRC screening procedure in the United States [6]. Numerous factors have led to this situation: colonoscopy allows for clear visualization of the entire colon, polypectomy may stop precancerous polyps from progressing to cancer, and clinicians may assess reasonable surveillance intervals based on the results of the index test [7]. Colonoscopy has benefits over other screening modalities, such as shorter intervals between tests and improved acceptability and tolerability of current sedation techniques. Despite its widespread availability, it is not considered inexpensive or readily accessible to the general public, making its use in mass screening difficult [8]. Multiple case-control and prospective cohort studies have shown that people who have a screening colonoscopy have a 68 percent to 88 percent lower cancer mortality rate than those who do not. A meta-analysis of retrospective studies found that, despite a 68 percent reduction in overall mortality, colonoscopy had little advantage in terms of cancer in the proximal colon [9]. Another study observed a 29% reduction in overall CRC mortality, a 47% reduction in mortality from distal CRC, and no reduction in mortality from proximal CRC. The above studies show that there is a significant reduction in the overall mortality rate, but these do not apply to all the areas, and there remains a lot of differences [10]. This distinction may be due to several factors influencing the consistency of the act itself (for example, an incomplete colonoscopy, the

gastroenterologist's level of training and experience, insufficient bowel preparation, or technical difficulties with polyp removal in the proximal colon) or variations in the biologic characteristics of proximal and distal colorectal cancers [11]. To fully resolve these concerns, evidence from large controlled randomized trials is still unavailable, although they are currently being performed [12]. Technical societies first supported screening colonoscopy in 1997, and Medicare beneficiaries were authorized for it in 2001. Unlike the faecal occult blood test (FOBT) and flexible sigmoidoscopy, which are backed by RCTs, the use of screening colonoscopy is focused on less-reliable indirect evidence from flexible sigmoidoscopy tests, observational studies, and case-control studies [13]. The United States Multi-Society Task Force on colorectal cancer recently revised its 2006 post polypectomy guidelines, taking into account the interim publication of several related studies, the emergence of serrated lesions, and concerns about decreased right-sided defense. Overall, the updated guideline supports the risk-stratification model based on baseline colonoscopy results, which was developed in 2006, and especially upholds the validity of the 10-year surveillance interval recommended in average-risk individuals after a negative screening colonoscopy. Surveillance guidelines for serrated lesions are also adopted, which are based on a risk-stratification approach [14].

FLEXIBLE SIGMOIDOSCOPY

Periodic screening is the most promising approach for lowering the burden of colorectal cancer. Because of the sensitivity of flexible sigmoidoscopy in detecting early cancers and adenomas, it has been widely recommended at three to five-year intervals. For family doctors, this examination is thought to be a cost-effective intervention [15]. Flexible sigmoidoscopy is also used to screen for colorectal cancer regularly. For people at average risk, most organizations recommend screening every three to five years, starting at age 50. Endoscopic maneuvering, colorectal anatomy, and pathologic recognition require extensive training. After 10 to 25 precepted sessions, most doctors report feeling comfortable performing the procedure without supervision [16]. The sigmoidoscope is inserted through the anus and distal rectum, and the scope tip is advanced into the sigmoid colon during the process. The long flexible sigmoidoscope was inserted between 48 and 55 cm deep on average. The sigmoidoscope is believed to be able to detect about 60% of all colorectal cancers [17]. The three- to five-year screening interval recommendation is based in part on estimates that an adenoma will progress to malignancy in seven to ten years. For people of average risk, most organizations recommend starting sigmoidoscopy screening at the age of 50 [18].

Other than its advantages and its effectiveness, flexible sigmoidoscopy also

CHAPTER 10

Recent Theranostics in Treatment of Colorectal Cancer

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Abstract: Colorectal cancer (CRC) is the common form of cancer occurring worldwide, having a high occurrence rate and also high mortality (death) rate. Chemotherapy and conventional approaches to treat CRCs are outdated and newer strategies are required to combat colorectal cancer. Neoadjuvant therapies have also shown some promise but have some major side effects, like building up intrinsic resistance and systemic toxicity problems associated with such therapies. Cancer nanomedicine, a rapidly developing interdisciplinary research field, is one of the new strategies being developed to address these issues. The use of nanoparticles and nanotechnology in cancer medicine has exploded in popularity over the last few decades. This is due to nanoparticles' suitable physical and chemical properties for *in vivo* applications. Cancer nanomedicine has been extensively studied in preclinical and clinical settings for targeted drug delivery and imaging. Nanomedicine, along with the theranostic approach, has been proposed as a novel way to improve CRC diagnosis and treatment.

Keywords: Nano-formulations, Nanoparticles, Prodrugs, Theranostics.

INTRODUCTION

Colorectal cancer is one of the most widely occurring cancers both in males and females. The yearly deaths caused by colorectal cancer account for about 10% worldwide. The overall 5-year survival rate in colorectal cancer is around 65%, with longer period survival in the past decades only modestly increased [1]. Blood in the stools, abdominal discomfort and pain, weight loss, and asthenia are the major indications associated with it. The risk factors in colorectal cancer could be environmental and genetic factors or a combination of both [2]. While genetic factors account for a minority of cases, there is a clear correlation between a positive history and an increased incidence of colorectal cancer. The so-called

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adenoma-carcinoma sequence, a multi-stage mechanism, is the dominant carcinogenic mechanism model for colorectal cancer [3]. Specific series of events are there in the initiation and development of tumors. Three mechanisms tend to be mainly based on CRC-related genetic alterations: chromosomal instability, high microsatellite instability, or CpG island phenotype methylator [4].

The screening and diagnosis of the colorectal cancer population are made with lots of diverse techniques. Faecal checks are employed to check blood in the stool in people who have no symptoms [5]. Immunochemical faecal occult blood test (iFOBT) and guaiac-based faecal occult blood test (gFOBT) are primarily used in screening programs for low-invasive studies [6]. More specificity is ensured by a stool DNA test, which looks for unique DNA mutations. Blood-based screening tests are useful for diagnosis, such as the identification of CEA antigen, the most well-known CRC tumor marker [7]. The FDA has recently approved the use of some novel techniques, such as CellSearchTM, to detect circulating tumour cells; however, these techniques are expensive and routinely not easy to implement [8]. Colonoscopy is reserved for symptomatic patients or is used only as a second-line procedure for routine screening of fecal test-positive patients. However, this technique is invasive, has some patient compliance concerns, and has some risks, like using anesthesia and possible cell or organ damage [9]. Alternative methods, such as barium enemas for X-ray rectal outlining or more complete techniques, including virtual colonoscopy and computed tomographic colonography, are available if this method is not feasible, but they involve colon cleaning before the examination and may detect non-neoplastic anomalies [10]. The introduction of nanomedicines is important for the effective treatment of any cancer. Not only in a therapeutic way, but nanomedicines are also used alternatively in a very potential way as a diagnostic tool. When these diagnostics nanomaterials are combined with therapeutics, they offer a very less toxic theranostic pathway [11].

NANOFLATFORMS FOR DRUG DELIVERY AND THERANOSTICS

Various tumour tissues are generally being identified as the cancer of the breast, colon, rectum, prostate, brain, *etc.*, but these all tissues are permeable to nanomedicines and nanoparticles [12]. Nanoparticle and nano-molecule drug delivery mechanisms can be divided into active and passive targeting. Active targeting strongly depends on the interaction between the target cell receptors and nanoparticles, while passive targeting relies on a variety of factors, such as longer biological half-life, long-circulating period at tumour locations, and the flow rate of nanoparticles to the disabled lymphatic system [13]. The EPR effects play a vital role and pose a serious issue for any nanomedicine or nanoformulation, which rapidly increases the uptake of these nanomedicines from the systemic circulation by macrophages, and therefore, the nanoparticles are cleared at a very

rapid rate from the body [14]. Targeted nanoparticles are currently one of the key methods for CRC therapy in preclinical development as a drug delivery mechanism based on monoclonal antibodies. There are different approaches for theranostics, and some are explained below [15].

NANOLIPOSOMAL BASED THERANOSTIC NANOPARTICLES

In 1961 Bangham *et al.* introduced the first therapeutic nano-platform used in medicine. This nano-platform was built on liposomes, which are the nanovesicular carriers and also the first clinical drug delivery system approved by the FDA for clinical use [16]. One of the widely used nanoparticles for the delivery of small peptides, nucleic acids, and proteins in nano-platform drug delivery is liposome-based nanoparticles. At the cellular level, nanoliposomes are known as one of the most powerful drug delivery mechanisms. This is primarily due to their size, ability to incorporate different substances, and characteristics of slow-release and targeting, which often contribute to lesser side effects [17]. Liposomes are now widely used as therapeutic nanocarriers, and they are also used in diagnostic tooling. The use of liposomes for molecular diagnosis is now a widely studied topic; the use of liposomes can be used for the diagnosis of various life-threatening diseases, like cancer, and various nondegenerative diseases, like Alzheimer's, *etc.* The liposomes' work involves the covalent binding of liposomes with peptides, antigens, and antibodies. While the formulation of such specialized liposomes that respond to the external stimuli are also in research progress and are now formulated, showing dormant results in neuro-imaging and diagnostic research [18].

Generally, this liposomal system can be classified into 3 main types:

1. Stealth Liposomes – These are large vesicular carriers and can be unlayered or multi-layered vesicles with some modified structure like added Polyethylene glycol (PEG) and or gangliosides to bypass the RES system by avoiding blood plasma opsonin protein which directly binds to the liposomal surface thereby inhibiting their activity.
2. Active liposomes – These liposomes are used for targeting specific moieties like receptors, proteins, peptides, hormones, antibodies, *etc.*
3. Sensitive liposomes – These are specialized types of liposomes with unique properties and be further subdivided as pH-sensitive, thermo (temperature) sensitive, and magnetic liposomes [19].

An example of an FDA-approved nanoliposome for colorectal chemotherapy is doxorubicin (Doxil®)-liposome Doxil is around 100 nm, and although it has much less gastrointestinal and cardiac toxicity, other side effects such as redness and

CHAPTER 11

Management of Colorectal Cancer

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Abstract: Management of colorectal cancer is a very important part of treatment as improper procedures may cause certain complications. Many decisions regarding the treatment depend on the condition of the tumour and the patient, and also the focus is on the treatment to be perform without complications. Management is done by first preparing the patient with different procedures, like stomal therapy, bowel preparation, or nutritional intervention. Then, the tumour is further evaluated, and accordingly, the treatment option is selected. Possible treatment options could be electrocoagulation, touch radiotherapy, local excision with or without neoadjuvant/adjuvant therapy; they all are local treatment methods for rectal cancer and endoscopic treatment. The results may vary with the selection of the procedure and the prognosis.

Keywords: Colorectal cancer, Electrocoagulation, Endoscopic treatment, Local excision, Stomal therapy, Tumour evaluation.

MANAGEMENT OF COLORECTAL CANCER

Kilian G M Brown *et al.*, reported that in high-income countries, the occurrence and mortality rates are higher for colorectal cancer [1]. Primary care physician plays a very vital role in coordinating when the multimodal management strategies are considered for colorectal cancer [2].

For primary confirmation, the endoscopic biopsy is further correlated with histology. Also, at the clinical-stage, identification is important. Primary care physicians can provide some prognosis and management guide. Computed tomography (CT) scan of the pelvis, abdomen, and chest is suggested in the UK and Australia to have Australia to have better understanding of the disease spread and condition. [3]. The stages are based on the magnitude of regional tumour incursion (T Stage), engagement of lymph nodes (N stage), and distant metastases (M Stage). The past diagnosis reports or imaging can be investigated for under-

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standing the metastases with further analysis of patients' blood for electrolytes, blood component count, and renal functioning. For post-treatment analysis, the disease surveillance is carried out with baseline carcinoembryonic antigen (CEA) [4].

A specialist investigation by an oncologist or surgeon would be necessary. The investigation is carried out with an MRI of the liver because detection of IV contrast medium with a CT scan is not possible in some patients. Initiation investigation with a CT scan or MRI is the choice of the patient who has rectal cancer. The use of MRI provides accurate staging investigation [5].

HOW CAN YOU PREPARE PATIENTS FOR SURGERY?

In primary care, many aspects related to preoperative assessment are taken care of. A preoperative optimization process is most often coordinated by colorectal cancer preadmission or preoperative examination clinics. However, this varies by healthcare environment [6].

Enhanced Recovery After Surgery (ERAS)

This consists of the standard care within preoperative management for patients undergoing colorectal operations. Variations can be seen in different institutions in the protocols of ERAS. Early mobilization, anesthetic practice, enteral nourishing, improving preoperative dietary position, education, counseling, and postoperative analgesics are all examples of postoperative management. With these protocols, the patients' stay can be shorten and complications can be reduced [7].

Stomal Therapy

Some patients may or may not require a temporary or permanent stoma after colorectal surgery. Due to some complications that get created due to the stoma like retraction, dermal abrasion, and parastomal herniation. The stoma formation is affected by factors like the stage, size, and location of the tumour; treatment; patient condition, and emergency surgery need. The low or mid rectal tumour may need a short-term ileostomy. This therapy is optional and can be picked up if desired by the patient. However, the stomal therapist needs to examine and also select an appropriate location for stoma [8].

Bowel Preparation

For administration of oral laxative, a solution is being utilized and a clear fluid diet is given preoperatively for at least 24 hours. For colonic resections, this is not much favored by the surgeons. In several studies, it has been indicated that post-

operative infections can be treated with mechanical bowel preparation and antibiotics. Though there is some ambiguity, current UK guidelines warn against frequently adopting mechanical bowel preparation before colorectal cancer resections, so they do note that it can be beneficial in patients undergoing rectal cancer restorative resection [9].

Nutritional Interventions

Malnutrition is common among cancer patients in terms of chemotherapy, radiotherapy, and surgery, as well as the metabolic consequences of cancer. Colorectal cancer patients are at a higher risk of malnutrition than most cancer patients. Patients with rectal cancer who undergo neoadjuvant chemoradiation have the highest rates. Though nutritional evaluation and support are systematically given before colorectal surgery, there is a deficiency of details on its potency. Preoperative carbohydrate loading is often considered in patients experiencing colorectal cancer surgery. On the day of surgery, a smooth, oral carbohydrate solution is delivered before midnight and again 2-3 hours before surgery [10].

LOCAL RECTAL TREATMENT OF RECTAL CANCER (CLINICS IN THE COLON A RECTAL)

Local treatment of rectal cancer remains a hot topic of discussion, with surgeons worried that a narrow approach that avoids a colostomy may decrease the possibility of cure. Despite improvements in surgical practice and the introduction of a multimodality approach to the treatment of rectal cancer that has increased sphincter-preservation rates, abdominal procedure are also associated with some morbidity and mortality. Cardiopulmonary compromise and collapse, anastomotic leakage and strictures, genital and urinary dysfunction, and clinical difficulties with defecation and continence are also complications of radical operations [11].

The lower morbidity associated with local therapy, along with the maintenance of normal bowel function after local excision, makes it a more appealing choice, helping to keep it on the rectal cancer care algorithm as a feasible option in the management of select rectum cancers. Furthermore, as we gain a greater understanding of the clinical behavior of the tumour and the prognostic importance of histologic grading and tumour characteristics, the use of local therapy in the treatment of rectal cancer will grow, ensuring its place as an alternative to radical surgery [12].

Tumor Evaluation

A systematic assessment of the patient is critical in the design of an effective

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